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Health and Environmental Effects Profile for Maneb

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR MANEB

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16. ABSTRACT

The Health and Environmental Effects Profile for Maneb was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Maneb has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for Maneb is 5×10^{-3} mg/kg bw/day for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

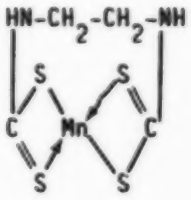
ADI	Acceptable daily intake
ChE	Cholinesterase
DNA	Deoxyribonucleic acid
ETM	Ethylenethiuram monosulfide
ETU	Ethylene thiourea
FEL	Frank-effect level
GI	Gastrointestinal
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
LT_{50}	Time lethal to 50% of recipients
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
ppt	Parts per trillion
TLC	Thin-layer chromatography

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Maneb is the common name for manganese [[1,2-ethanediylbis(carbamodithioate)](2-)]-complex, formerly [1,2-ethanediylbis[carbamodithioato](2-)] manganese and [ethylenebis[dithiocarbamate]] manganese (BCPC, 1977). This compound is also known as 1,2-ethanediylbiscarbamodithioic acid-manganese complex; 1,2-ethanediylbismaneb-manganese (2+) salt(1:1); ethylenebis-(dithiocarbamato)-manganese; ethylenebis(dithiocarbamic acid)-manganese salt; 1,2-ethylenediylbis(carbamodithioato) manganese; manebe; manganese ethylene bisthiocarbamate, among others (IARC, 1976; NIOSH, 1983).

Maneb was introduced in 1950 under the trade name of Manzate by E.I. du Pont de Nemours and Co. and under the trade name Dithane M-22 by Rohm and Haas Company (Sanborn et al., 1977; BCPC, 1977). Maneb is also known by numerous other trade names including Chem Neb, Chlorable M, Kypman 80, Maneb 80,. Maneba, Manam, Manebgan, Manesan, Polyram M, Rhodianebe, Sopranebe, Sup 'R Flo, Tremangol, Tubothane, Vancide, and others (IARC, 1976; NIOSH, 1983). The structure of maneb is given below (IARC, 1976):



Molecular formula: $C_4H_6MnN_2S_4$

Molecular weight: 265.3

The Chemical Abstracts Service (CAS) Registry Number for this compound is 12427-38-2.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Pure maneb is a yellow, crystalline solid; the technical product is a light-colored solid (BCPC, 1977; Sanborn et al., 1977). Maneb has the following physical properties:

Melting Point:	Decomposes before melting (BCPC, 1977; Sanborn et al., 1977)
Vapor Pressure:	"Negligible" (no numerical value given) (Hann and Jensen, 1977)
Specific Gravity:	1.92 (Hann and Jensen, 1977)
Solubility:	Moderately soluble in water (Hann and Jensen, 1977) insoluble in most organic solvents (BCPC, 1977) soluble in chloroform and pyridine (IARC, 1976)
Stability:	Unstable in the presence of moisture or acids (BCPC, 1977; Sanborn et al., 1977)

1.3. PRODUCTION DATA

Maneb is produced by the following companies (SRI, 1983):

Producer	Location
Blue Spruce Co.	Bound Brook, NJ
E.I. du Pont de Nemours and Co., Inc.	LaPorte, TX
Rohm and Haas Co.	Philadelphia, PA

It has been estimated that 12 million pounds of maneb were produced in 1972. Maneb is prepared by reacting the condensation product of ethylenediamine, carbon disulfide and sodium hydroxide with manganese sulfate (von Rumker et al., 1974).

1.4. USE DATA

Maneb is a protective, broad spectrum contact fungicide used on vegetable, fruit, nut and grain crops, and on turf grasses to control blight, rust, bunt, mildew and other fungus diseases (von Rumker et al., 1974).

2. ENVIRONMENTAL FATE AND TRANSPORT

Data for the fate and transport of maneb in soil are available from both laboratory and field studies. Helling et al. (1974) studied the mobility of maneb in a variety of soil types on thin layer chromatography (TLC) plates. An 80% maneb (100 µg active ingredient) preparation applied to TLC plates of Hagerstown silty clay loam (2.5% organic matter content, 39.5% clay, pH 6.8, water content at 1/3 bar 34.1%) had an overall average R_f of 0.33 when visualized by bioassay using 10 different species of fungi and 1 alga. Maneb was found to have a strong origin spot and limited streaking. The investigators interpreted the greater mobility of maneb when compared to that of zineb (R_f = 0.01) to be due to dissociation of manganese, with the resultant movement of free ethylenebis (dithiocarbamate). The R_f values for 1 µg of maneb on soil TLC plates with five soil types were as follows (the organic matter content is given in parentheses): 0.42 on Norfolk sandy loam (0.14%); 0 on Lakeland sandy loam (0.90%); 0.22 on Hagerstown silty clay loam (2.5%); 0.14 on Barnes clay loam (6.9%) and 0 on Celeryville muck (90.4%). Autoradiographic studies of mobility using ^{14}C-maneb revealed the presence of numerous impurities (zineb was contaminant-free), one of which had an R_f identical to that of ethylene thiourea (ETU). The conclusion reached was that maneb was slightly more mobile than zineb.

The mobility of maneb in soil was studied by Nash and Beall (1980) when the fungicide was sprayed onto tomato plants growing in Galestown sandy loam (pH 6.7, organic matter content 5.2%) in microagroecosystem chambers. Maneb, detected as ethylenediamine, was present on the soil surface throughout the 70-day duration of the experiment. It did not penetrate below 1 cm depth, but dissipated with a half-life of 36 days. The concentration of ethylenediamine in leachate water was only 1.2 µg/ℓ.

In a field study in Delaware, Rhodes (1977) found that when ^{14}C-maneb was applied at a rate of 2 lb/acre to 4-inch diameter sections of soil (Keyport silty loam) isolated by 12-inch long sections of stainless steel tubing driven into the ground (runoff was prevented by a protruding lip), the total ^{14}C residues disappeared with a half-life of 4-8 weeks. Total rainfall for this period was 1-11 inches. Radiolabeled residues were leached to about a 5-inch soil depth and after 52 weeks (total rainfall = 51 inches) 26.5% of the applied radioactivity was still present in the top 1 inch.

From the above studies it appears that maneb, or some degradation product of maneb, is somewhat mobile in soil, but not to any great extent. The strong origin spot on soil TLC plates in the Helling et al. (1974) study indicates that the active fungicide adsorbed strongly to the soil and would not likely be found in groundwater.

The fate of maneb in soil also depends upon its ability to volatilize. Since water solubility of maneb is considered to be moderate and the vapor pressure negligible (value not given) (Hann and Jensen, 1977), volatilization is probably not a major removal route. This is reflected in the previously described microagroecosystem study by Nash and Beall (1980). Air concentrations of maneb, measured as ethylenediamine, in the chambers were <10 ng/m^3 at day 0, although the soil and leaf (tomato plants) concentrations of maneb were ~0.4 and 60 mg/kg, respectively.

The oxidative degradation of maneb in soil was studied by Hylin (1973), who mixed 20 mg of maneb with 100 g of soil at pH 7, passed moist air through the mixture, and measured the evolution of carbon disulfide (CS_2). Only 5 µmoles of CS_2 evolved after 10 hours compared with 25 µmoles of gas after 7 hours when maneb was suspended in aqueous media at the same pH.

Thus, oxidation of maneb in soil may be slower than the oxidation in aqueous suspensions but it still may represent one of the routes of degradation of this compound in soil.

Very little information was available on the degradation of maneb by microbes in the soil. Microbial degradation may represent a minor route, however, since maneb is hydrolytically decomposed by moisture present in soils (Sanborn et al., 1977).

The microbial metabolism of 5,6-dihydro-3H-imidazo(2,1-c)-1,2,4-dithiazole-3-thione has been investigated. This chemical, a product of the spontaneous degradation of maneb, is commonly known as ethylenethiuram monosulfide (ETM). ETM was metabolized microbially to produce ETU (Vonk and Sijpesteijn, 1976), a carcinogen in animals (IARC, 1974, 1982). ETU was degraded to ethyleneurea and CO_2 both chemically and microbially within 4 days in soil (Kaufman and Fletcher, 1973).

The persistence of maneb in soil was studied by Chinn (1973) using several species of fungi as bioassay. When maneb was applied at 100 ppm (based on dry weight of soil), fungicidal activity persisted for 1 week; at 1000 ppm, fungicidal activity persisted for 11 weeks, although levels of active fungicide had dropped considerably within 4 weeks.

The main route of entry of maneb into aquatic media would probably be through suspended particles in runoff water, consistent with the experimentally observed tendency to sorb to particulate matter. The fate of maneb in water will depend upon its ability to undergo hydrolysis, oxidation, photodegradation, volatilization and microbial degradation.

Hylin (1973) reported that when 20 mg of maneb was suspended in 100 mℓ of phosphate buffer at pH 7 and air was drawn through the system, measurable CS_2 was detected after 30 minutes and reached a level of ~25 μmoles within 7 hours. At pH 6, CS_2 levels reached 30 μmoles within 4 hours.

Degradation products identified in the aqueous suspension were ETU, ETM, sulfur and etylenediamine. Nitrogen gas substituted as carrier prevented the degradation of maneb in aqueous suspension. In contrast, Viel and Chancogne (1964) found that 0.3 g of maneb suspended in deionized water at pH 8, and kept under an atmosphere of nitrogen, was hydrolyzed by 50% in 20 days at 20°C, and in 5 hours at 76°C. Difficulty in excluding oxygen from the system may account for this seeming contradiction. Muskat and Schlemmer (1976) reported that 330 µg of maneb suspended in water was reduced to 326 µg in 5 minutes and 220 µg in 3.5 hours. ETM and ETU concentrations increased accordingly.

Muskat and Schlemmer (1976) presented the only data encountered on the photodegradation of maneb. When aqueous suspensions sprayed onto filter paper were exposed to ultraviolet light (wavelength not reported) under moist conditions, all the maneb was converted to ETU within 5 days.

Maneb is not likely to volatilize from water due to its negligible vapor pressure (Hann and Jensen, 1977). No information was encountered on microbial degradation; however, since maneb is readily degraded by hydrolysis, oxygen and light, microbial degradation in the aquatic environment is difficult to measure.

One of the products of maneb degradation is ETU, but ETU is readily photodegraded in aqueous media to ethyleneurea, hydantoin and glycine sulfate (Cruickshank and Jarrow, 1973; Rhodes, 1977). In drainage ditch water, ETU was degraded 90% by sunlight in 24 days (Ross and Crosby, 1973).

Information regarding the fate and transport of maneb in air is limited. Maneb has a negligible vapor pressure and it is not likely to volatilize to a large extent. Nash and Beall (1980) found the air concentration of maneb (detected as ethylenediamine) to be only ~10 ng/m³ at day 0 in the

previously described microagroecosystem chamber. The major routes of entry of maneb into the atmosphere are more likely to be spray drift during application and drift in wind of maneb sorbed to soil particles. The extent of degradation in air will depend upon moisture content, temperature, photodegradation and oxidation. The half-life of maneb in air has been determined to be 7-14 days (Nash and Beall, 1980).

3. EXPOSURE

No monitoring data for maneb were contained in STORET, and no other information regarding ambient levels of maneb in soil, water or air was encountered.

Exposure of humans to maneb is primarily through residues on food. Duggan et al. (1966) monitored food for pesticides using the "total diet" approach (all the food consumed over a 2-week period by an 18-year-old male). These investigators collected 82 foods from 18 markets in Boston, MA, Kansas City, MO, and Los Angeles, CA, separated them into 12 classes and composited them into a slurry. Of the 216 composites analyzed, 5 were found to contain dithiocarbamate residues ranging from 0.4-0.8 ppm calculated as equivalent zineb concentrations. These foods were mainly grain and cereal products and raw and processed leafy vegetables. In addition to exposure through residues on food, humans involved in applying maneb to crops or humans in the vicinity of such application may also be exposed.

Concern over exposure to maneb residues on food is enhanced by the increased levels of ETU found in cooked and processed foods. Very little, if any, ETU was found on harvested apples, tomatoes, grapes, pears, potatoes, cucumbers, squash or cantaloupes; however, the acts of cooking, processing or storing such foods have resulted in detectably increased levels of ETU (Ross et al., 1978; Ripley and Cox, 1978; Ripley et al., 1978; Ripley and Simpson, 1977; Pease and Holt, 1977; Watts et al., 1974).

4. COMPOUND DISPOSITION AND PHARMACOKINETICS

4.1. ABSORPTION

Explicit details regarding the absorption of maneb, such as blood plasma levels or absorption kinetics, were not found in the available literature. Based on metabolism, distribution and excretion data, however, it can be inferred that maneb is absorbed to some extent from the GI tract following oral administration to rats and mice (Brocker and Schlatter, 1979; Seidler et al., 1970; Jordan and Neal, 1979).

Brocker and Schlatter (1979) administered [^{54}Mn]maneb to two female rats via gastric intubation at a level of 2×10^{-5} mol/kg, and observed 96.8 and 94.3% of the administered doses of radioactivity in the feces within 20 hours following dosing. Considering the high [^{54}Mn]-activity in the feces and residual [^{54}Mn]-activity in the liver (2.84×10^{-3} and 4.46×10^{-3} of the administered [^{54}Mn]-dose/g wet tissue), the authors concluded that Mn(II) was not absorbed to a great extent from the intestine, and most of that which was absorbed was trapped by the liver and subsequently excreted into the intestine via the bile duct. Brocker and Schlatter (1979) reported greater absorption of [^{14}C]maneb (location of radiolabel not specified) than [^{54}Mn]maneb from the GI tract. These differential absorption rates may be due to the phenomenon of acid hydrolysis observed by Seidler et al. (1970), in which hydrolysis of [^{14}C]maneb yielded ethylenediamine and carbon disulfide under acid conditions similar to those present in the stomach. It appears that acid-hydrolyzed organic [^{14}C]-metabolites are readily absorbed through the GI tract, while inorganic [^{54}Mn]-metabolites are not absorbed via the GI tract, but rather are excreted almost entirely in the feces.

4.2. DISTRIBUTION

Seidler et al. (1970) administered [^{14}C] maneb (location of radiolabel not specified) in a single oral dose of 390 mg/kg body weight to rats. On days 1 and 5 after treatment, 1.2 and 0.18%, respectively, of the administered dose was detected as metabolites of maneb in the thyroid gland, liver, kidneys, spleen and brain. Further details were not discussed in the available abstract of this study.

Following single oral administration via gastric intubation of [^{54}Mn]maneb to two female rats at a level of 2×10^{-5} mol/kg, Brocker and Schlatter (1979) detected residual [^{54}Mn]-activity in the liver and kidneys of the treated animals. Expressed as the fraction of the [^{54}Mn]-dose administered/g wet tissue, the residual activities in the liver of individual animals were 2.84×10^{-3} and 4.46×10^{-3}, while the residual activities in the kidneys were 1.51×10^{-3} and $<1.23 \times 10^{-3}$.

4.3. METABOLISM

Following oral administration of a single dose of 390 mg [^{14}C]maneb/kg body weight to rats, Seidler et al. (1970) detected ethylenediamine, ethylene bisthiuram monosulfide (a synonym for ETM), and ETU as metabolites of maneb in the urine and feces of treated animals. Within 24 hours post-dosing, 49.5% of the administered dose was excreted in the urine and feces in the form of ethylenediamine, ETM and ETU; by day 5 post-dosing, 55% of the administered dose was present as these metabolites in the urine and feces of treated animals.

Jordan and Neal (1979) administered [^{14}C]maneb suspended in 0.15 mℓ of olive oil to adult male ND/4(s)BR mice via gavage at dose levels of 0.05 and 0.25 mmol/kg. At the higher dose level, the majority of [^{14}C]-activity detected in the urine (77.8%) was unidentified polar metabolites; identified metabolites included ETU (15.8%) and ethyleneurea (4.0%).

Unidentified polar metabolites comprised 82.4% of the radioactivity in the urine of mice given [^{14}C]maneb at a dose level of 0.05 mmol/kg, while ETU (7.8%) and ethyleneurea (6.8%) were also detected as urinary metabolites. [^{14}C]Maneb was not metabolized to [^{14}C]carbon dioxide or [^{14}C]ethylenebisdiisothiocyanato sulfide.

4.4. EXCRETION

Seidler et al. (1970) administered single oral doses of [^{14}C]maneb to rats at a dose level of 390 mg/kg. Within 24 hours post-dosing, 49.5% of the administered dose was excreted as metabolites in the feces and urine, while 55% was excreted as metabolites in the feces and urine within 5 days after treatment. Approximately 33% of the recovered [^{14}C]-activity was excreted in the urine and ~67% was excreted in the feces.

Brocker and Schlatter (1979) reported that >99% of an administered single oral (gastric intubation) dose of 2×10^{-5} mol/kg [^{14}C]maneb was recovered in the urine and feces of two female rats within 72 hours after treatment. Recoveries of [^{14}C]-activity in the urine were 48.5 and 41.0%, recoveries in the feces were 63.2 and 53.7%, and recoveries in exhaled air were 0.24 and 0.60%. Brocker and Schlatter (1980) further observed that excreted [^{14}C]-activity in the urine of rats was independent of the [^{14}C]maneb dose given. Over a single oral dose range of 23 µg to 1.4 g [^{14}C]maneb/kg body weight, excretion data from 39 female rats indicated that ~50% of the administered radioactivity was excreted in the urine.

Brocker and Schlatter (1979) administered a single oral dose of [^{54}Mn]maneb via gastric intubation at a level of 2×10^{-5} mol/kg to two female rats. Within 20 hours after dosing, 94.3 and 96.8% of the [^{54}Mn]-activity was excreted in the feces of the two treated animals.

Jordan and Neal (1979) administered [^{14}C]maneb (location of radiolabel not specified) as a single gavage dose of 0.05 or 0.25 mmol/kg body weight to adult male ND/4(s)BR mice. Of the total [^{14}C]-activity excreted in the urine and feces at the lower dose level, 68.5 and 31.5% were detected on days 1 and 2, respectively, after treatment. At the higher dose level, 83.9% of the recovered [^{14}C]-activity in urine and feces was excreted within 24 hours after dosing, while the remaining 16.1% was excreted between 24 and 48 hours post-dosing. At both dose levels, >90% of the [^{14}C]-activity recovered within 48 hours was detected in the feces and <10% in the urine of treated animals. The majority of [^{14}C]-radioactivity excreted in the urine was unidentified polar metabolites; lesser amounts of radiolabeled ETU and ethyleneurea were also present in the urine. [^{14}C]Maneb was not excreted via the lungs as [^{14}C]carbon dioxide and no radiolabeled ethylenebisdiisothiocyanato sulfide was detected in the urine.

5. EFFECTS

5.1. CARCINOGENICITY

No significant increase in tumors was observed in (C57BL/6 x C34/Anf)F_1 or (C57BL/6 x AKR)F_1 mice following administration of the maximum tolerated dose (MTD) of maneb via a combination of gavage and diet (Innes et al., 1969; BRL, 1968). Groups of 18 male and 18 female mice of each strain were given gavage doses of maneb in 0.5% gelatin at a level of 0 or 46.4 mg/kg/day for 3 weeks, and subsequently were given dietary concentrations of maneb at 0 or 158 ppm, respectively, ad libitum for 81-83 weeks. The MTD was not adjusted for body weight changes during the gavage phase of this study, but was adjusted before the dietary phase was initiated. For strain (C57BL/6 x C3H/Anf)F_1, the number of male tumor-bearing animals was 2/18 as compared with 22/79 for controls, and the number of female tumor-bearing animals was 0/17 as compared with 8/87 for controls. For strain (C57BL/6 x AKR)F_1, the number of male tumor-bearing animals was 4/18 as compared with 16/90 for controls, and the number of female tumor-bearing animals was 3/18 as compared with 7/82 for controls. For both sexes of animals, there was no significant difference between either treated strain of mice and their respective controls in the incidence of reticulum cell sarcoma, malignant lymphoma, pulmonary adenoma, pulmonary carcinoma, hepatoma, mammary carcinoma or gastric papilloma.

Groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 and (C57BL/6 x AKR)F_1 mice were given a single subcutaneous dose of maneb in 0.5% gelatin at a level of 0 or 100 (MTD) mg/kg, and subsequently were observed for 18 months (BRL, 1968). There was no significant increase in the number of animals with tumors for either strain of treated animals. For strain (C57BL/6 x C3H/Anf)F_1, the number of male tumor-bearing animals was 2/17 as compared with 27/141 for controls, and the number of female tumor-bearing

animals was 0/18 as compared with 9/154 for controls. For strain (C57BL/6 x AKR)F_1, the number of male tumor-bearing animals was 1/18 as compared with 8/161 for controls, and the number of female tumor-bearing animals was 1/17 as compared with 17/157 for controls. For both sexes of animals, there was no significant difference between either treated strain of mice and their respective controls in the incidence of reticulum cell sarcoma, malignant lymphoma, pulmonary adenoma, pulmonary carcinoma, hepatoma, mammary carcinoma or gastric papilloma.

In what appears to be a pulmonary adenoma assay, strain A mice (number not reported) and 200 C57BL mice were given gavage doses of 0 or 500 mg maneb/kg body weight, 6 times/week, for up to 9 months (Balin, 1970). A representative number of animals of each strain were killed at unspecified intervals up to 9 months, at which time all surviving animals were killed. Of 42 C57BL mice surviving to 9 months, 4 had pulmonary adenomas (not significant, $p>0.05$), whereas 0/44 control animals developed pulmonary adenomas by 9 months. For the strain A mice, 23 treated animals of 42 surviving to 9 months developed pulmonary adenomas, a statistically significant ($p<0.01$) number when compared with control incidence (12/45). Chernov et al. (1972) also observed an increased incidence of lung adenomas in mice following oral administration of the MTD of maneb; further details concerning duration, dose level, controls and tumor incidences were not reported in the available abstract.

Maneb exhibited weak blastomogenic activity when administered orally to rats at a dose of 500 mg/kg, 1 time/week, for 6 months (Balin, 1970). Treated animals were observed to have some lung adenomas (especially in the subpleural region), hemodynamic changes, and destructive and dystrophic hepatic lesions. Details regarding controls and tumor incidences were not reported in the available abstract.

Andrianova and Alekseev (1970) administered maneb orally via gavage at a dose level of 335 mg/kg to 60 rats 2 times/week for life (up to 22 months). Of 6 animals surviving at 22 months, 1 had subcutaneous rhabdomyosarcoma and 1 had mammary carcinoma. One fibrosarcoma was observed in 1/46 untreated controls surviving at 22 months. Results of statistical tests of significance were not reported in the available abstract or in the summary of this study by IARC (1976).

Andrianova and Alekseev (1970) also administered single doses of maneb in paraffin via subcutaneous injection to 48 rats at a dose level of 12.5 mg/kg, and observed the animals for life (up to 22 months). By 22 months, 3/4 surviving treated animals had malignant tumors, including 2 fibrosarcomas and 1 thyroid carcinoma. One fibrosarcoma was observed in 1/46 untreated controls surviving at 22 months. Results of statistical tests of significance were not reported in the available abstract or in the summary of this study by IARC (1976).

IARC (1976) did not make a determination regarding the carcinogenicity of maneb in experimental animals or humans when it initially evaluated this chemical. Equivocal results obtained for the incidence of lung adenomas in four strains of mice and the small number of rats surviving treatment in the available carcinogenicity assays precluded an evaluation of the carcinogenicity of maneb in experimental animals. No data regarding the carcinogenicity of maneb in humans are available. Maneb is not considered by IARC (1982), in its more recent evaluation, to be a chemical for which there is sufficient evidence of carcinogenicity in experimental animals.

5.2. MUTAGENICITY

The genotoxicity of maneb has been tested in various bacteria, yeast, Drosophila melanogaster, and mammalian cell assays. These tests are summarized in Table 5-1.

TABLE 5-1

Mutagenicity Testing of Maneb

Assay	Indicator Organism	Application	Concentration or Dose	Activating System	Response*	Comment	Reference
Reverse mutation	S. typhimurium TA1535 TA1537 TA1538 TA98 TA100	plate incorporation	10-1500 mg/plate	± S-9	- - - - -	NC	De Lorenzo et al., 1978
Reverse mutation	S. typhimurium TA1535 TA1537 TA1538 TA98 TA100	NR	NR	NR	"+" "+" "+" "+" "+"	Maneb exhibited weak mutagenic activity ("+") in all strains of S. typhimurium tested.	Warren et al., 1976
Reverse mutation	Escherichia coli Strain B	NR	NR	None	+	NC	Warren et al., 1976
Mitotic gene conversion	Saccharomyces cerevisiae Strain D-7	NR	NR	None	+	NC	Warren et al., 1976
Mitotic gene conversion	S. cerevisiae Strain NR	NR	5 ppm	None	+	NC	Guerzoni et al., 1976
Mitotic gene conversion	S. cerevisiae Strain D-4	maneb incubated with cells in media	750 ppm	None	-	NC	Siebert et al., 1970
Sex-linked recessive lethal	Drosophila melanogaster	larval feeding	0, 5, 10 or 15 mg maneb/100 ml food	None	-	At the 15 mg/100 ml level, there was a slight but not statistically significant increase in mutation frequency.	Vasudev and Krishnamurthy, 1980
Autosomal recessive lethal	Drosophila melanogaster	larval feeding	0, 5, 10 or 15 mg maneb/100 ml food	None	-	At the 15 mg/100 ml level, there was a slight but not statistically significant increase in mutation frequency.	Vasudev and Krishnamurthy, 1980
Inhibition of DNA synthesis	rat thymocytes	cell culture	0, 1, 10 or 100 µg/ml	None	+	42% inhibition of DNA synthesis at 10 µg/ml	Rocchi et al., 1980

TABLE 5-1 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activating System	Response*	Comment	Reference
Inhibition of scheduled DNA synthesis	human lymphocytes	cell culture	10 µg/mL	None	+	63% inhibition of scheduled DNA synthesis	Rocchi et al., 1980
Inhibition of unscheduled DNA synthesis	human lymphocytes	cell culture	10 µg/mL	None	+	58% inhibition of unscheduled DNA synthesis	Rocchi et al., 1980

*Responses: +, positive; -, negative; ±, negative with and without S9 activation system; $\underline{+}$, positive with and negative without S9 activation system; $\overline{+}$, negative with and positive without S9 activation system

NR = Not reported; NC = No comment

In the reverse mutation assay in Salmonella typhimurium, maneb was not mutagenic (De Lorenzo et al., 1978) or was weakly mutagenic (Warren et al., 1976) to tester strains TA1535, 1537, 1538, 98 and 100. Maneb, however, induced a significant number of reverse mutations in Escherichia coli-Strain B (Warren et al., 1976). Depending on the strain of Saccharomyces cerevisiae tested, maneb yielded both positive (strain D-7) and negative (strain D-4) activity in the mitotic gene conversion assay (Warren et al., 1976; Guerzoni et al., 1976; Siebert et al., 1970).

Vasudev and Krishnamurthy (1980) administered 0, 5, 10 or 15 mg maneb/100 mℓ food to Drosophila melanogaster by larval feeding. At the highest dose level, there was a slight, but not statistically significant, increase in mutation frequency of both sex-linked recessive lethals and autosomal recessive lethals.

Application of 10 μg maneb/mℓ media resulted in a 42% inhibition of DNA synthesis in rat thymocytes, a 63% inhibition of scheduled DNA synthesis in human lymphocytes, and a 58% inhibition of unscheduled DNA synthesis in human lymphocytes (Rocchi et al., 1980).

5.3. TERATOGENICITY

In a teratogenicity study consisting of three experiments, Petrova-Vergieva and Ivanova-Chemishanska (1973) administered maneb to pregnant white rats as either a single oral dose of 0, 0.5, 1.0, 2.0 or 4.0 g/kg on day 11 or 13 of gestation, or as repeated oral doses of 0, 125, 250 or 500 mg/kg/day for 20 days, starting on day 2 of gestation. In the first two experiments, Caesarean sections were performed on day 21 of gestation. For the purposes of this study, gross malformations were defined to include exencephaly, encephalocele, hydrocephalus, exophthalmus, cleft palate, cleft lip, micrognathia, retarded/clubbed forelimb or hindlimb, forelimb ectrodactyly/oligodactyly, hindlimb ectrodactyly or polydactyly, short kinked

tail and umbilical hernia. For animals dosed on day 11 of gestation, no significant effects were observed in dams exposed to 0.5 g/kg or their offspring, while a significantly increased incidence in the total number of grossly malformed fetuses ($p<0.001$) was observed at the 1.0, 2.0 and 4.0 g/kg levels. Significantly increased fetal mortality ($p<0.001$) was observed at the 2.0 and 4.0 g/kg levels administered on day 11 of gestation, and a significant increase in the number of resorptions ($p<0.001$) was also noted at the 4.0 g/kg level administered on day 11 of gestation. For animals treated on day 13 of gestation, no effect on dams or fetuses was observed at the 0.5 g/kg level, while a significant increase in the total number of grossly malformed fetuses ($p<0.001$) was noted at the 1.0, 2.0, and 4.0 g/kg levels. From these single dose experiments, 500 mg maneb/kg body weight was established as a NOEL, and, therefore, maneb was administered at dose levels of $\leq$500 mg/kg/day throughout gestation (days 2-21). At the 125 and 250 mg/kg/day dose levels, there was no effect on dams or fetuses; at the 500 mg/kg/day level, mean fetal body weight was decreased slightly, but there was no significant effect on the incidence of malformations (only 1 of 100 treated fetuses was malformed, as compared with 0 of 73 control fetuses). The authors noted that the dose levels that induced teratogenic effects were extremely high, equivalent to $\geq$1000 times the daily human intake that would result from ingestion of foods containing the maximum permitted residues of maneb (Petrova-Vergieva and Ivanova-Chemishanska, 1973).

Larsson et al. (1976) administered maneb by gavage at levels of 0, 400, 770 or 1420 mg/kg to pregnant NMRI mice on day 9 or 13 of gestation or to pregnant Sprague-Dawley rats on day 11 of gestation. Both species of animals were killed on day 18 of gestation. For the purposes of this study, gross malformations were defined to include cleft palate, brachygnathia, low

external ear, open eye, exophthalmia, anophthalmia or microphthalmia, exencephaly, hydrocephaly, meromelia, syndactlyly, adactyly or oligodactyly, clubfoot, short tail, umbilical hernia, edema and constriction of the neck region. Neither maternal toxicity nor treatment-related teratogenic effects on fetuses were observed in mice at any dose level tested. In rats, no fetal malformations were observed at the 400 mg/kg dosage level, but the frequency of resorption was increased. Increased incidences of resorptions and gross malformations were observed in the fetuses of rats treated at dose levels of 770 and 1420 mg/kg; all viable fetuses at both dose levels were malformed (i.e., 24/24 and 45/45, respectively) while only 1/102 viable control fetuses was malformed. Of the fetuses examined, 7/7 offspring of rats treated at the 770 mg/kg level and 2/2 at the 1420 mg/kg level had skeletal malformations, including fused ribs, malformed vertebral column and malformed extremities; 5/7 at the 770 mg/kg level and 10/10 at the 1420 mg/kg level had internal malformations, including hydrocephaly, malformed spinal cord, malformed eyes, dilated renal pelvis and internal hemorrhage. Of the control fetuses examined, 0/36 had skeletal malformations and 1/14 had internal malformation(s).

When increasing amounts of zinc acetate (0, 15, 30 and 60 mg/kg) were coadministered with maneb (750 mg/kg) to rats on day 11 of gestation, progressively reduced teratogenic effects were observed (Larsson et al., 1976; Larsson, 1976). Considering teratogenicity data of other dithiocarbamates that contain zinc, the authors hypothesized that the mechanism of maneb teratogenicity depends upon the availability of zinc, as maneb is a chelating agent with the capability of trapping zinc, an element that is required for many enzyme systems.

Chernoff et al. (1979) conducted both a teratogenicity study with rats and mice exposed to maneb *in utero* and a postnatal study with rats exposed to maneb *in utero* and via the milk of lactating dams. For the teratogenicity study, pregnant CD-1 mice were given gastric intubation of maneb at dose levels of 0, 375, 750 or 1500 mg/kg/day on days 7-16 of gestation, and pregnant Sprague-Dawley rats received gastric intubation doses of 0, 120, 240 or 480 mg/kg/day on days 7-16 of gestation. Mice were killed on day 18 of gestation and rats on day 21. For the postnatal study, maneb was administered by gastric intubation to pregnant Sprague-Dawley rats at levels of 0, 240 or 480 mg/kg/day from day 7 of gestation through day 15 postpartum. A significant dose-related increase in maternal liver-to-body weight ratio ($p<0.001$) and decrease in the number of fetal caudal ossification centers ($p<0.05$) were observed in treated mice. Maternal toxicity among treated rats, manifested in a significant dose-related decrease in weight gain ($p<0.001$) and increase in liver to body weight ratio ($p<0.001$), was noted. Effects were seen only at the 480 mg/kg/day level in rats and included significantly depressed fetal weight ($p<0.05$), significantly decreased degree of caudal ossification ($p<0.05$), and hydrocephalus in 18 fetuses from 4 of 29 litters. (No fetuses in 21 control litters had hydrocephalus.) In the postnatal study, statistically significant minor changes ($p<0.05$) occurred in neonates, including an increased female body weight on day 1 after birth and retardation of eye opening among males. No dose-related effect on parturition or litter size or change in behavior and development of rat neonates followed a combined perinatal and postnatal exposure to maneb (Chernoff et al., 1979; Kavlock and Chernoff, 1978).

Several teratogenicity studies were reported in the Russian literature; however, these studies were only available in abstract form and, therefore, little detail concerning experimental design and results was available.

When administered as a single oral dose during gestation or daily throughout gestation at a level of 0.25-4.0 g/kg to pregnant rats, maneb induced significant teratogenic and embryotoxic effects (Ivanova-Chemishanska et al., 1975a). Ivanova-Chemishanska (1971) reported embryotoxic and teratogenic effects in the fetuses of rats following oral administration of maneb at 1/20-1/5 of the LD_{50}. Matokhnyuk (1971) reported no embryotoxic effects in the offspring of rats exposed to maneb vapors at a concentration of 30 mg/m^3 during pregnancy (the exposure regimen was not reported).

Grolleau et al. (1975) sprayed maneb at a level of 10.0 kg/ha on Japanese quail eggs. No treatment-related histopathological changes were observed in chicks at birth, and there was no effect on the rate of hatching, anomalies and malformations of chicks, or on chicks 1 month after hatching.

5.4. OTHER REPRODUCTIVE EFFECTS

Several pertinent mammalian studies were published in the Russian literature. Only limited information was available in the English abstracts of these studies.

Ivanova-Chemishanska et al. (1975b) administered maneb orally to male and female rats at a dose equivalent to 0.002-0.1 of the LD_{50} (actual dose not reported), 2 times/week, for 4.5 months. Dose-related effects in treated females included stimulated follicular atresia, disturbed ovulation, disturbed maturation of Graafian follicles, and disturbed development of corpora lutea; altered levels of estrogens and progesterons resulted in disruption of the estrous cycle. In treated males, there was an absence of mature spermatozoids and decreased sperm motility and viability as a result of decreased levels of testicular androgens. Treatment of either males or

females resulted in a decreased number of term pregnancies; decreased fertility, gestation and lactation were observed in the successive two generations (F_1 and F_2).

Shtenberg et al. (1969) gave oral doses of maneb in sunflower oil to male and female rats at levels of 5, 10 or 30 mg/kg for 4, 7 or 11-12 months. Effects of altered spermatozoids and estrous cycle were reported to be dose dependent and increasingly severe with lengthened exposure. Treatment-related effects observed at the two highest dose levels included reduced fertility among females, increased incidence of stillbirths, increased fetal mortality up to 1 week after birth, reduced fetal body weights, and retarded fetal physical development. Unspecified reproductive effects also were noted in the third generation (F_2).

Decreased testicular activities of glucose-6-phosphate dehydrogenase and succinate dehydrogenase were observed in male rats given oral doses of maneb of 30 mg/kg/day for 11 months (Shtenberg et al., 1973).

Weppelman et al. (1980) did not observe any effect on egg production or reproductive organs of laying hens given 600 ppm of maneb in the diet for 7 days.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Sobotka et al. (1972) investigated the behavioral and neuroendocrinal effects of low dietary concentrations of maneb on young male Osborne-Mendel rats. Rats were exposed to 0, 0.5, 1.0 or 10 ppm of maneb (either directly, or for neonatal rats, by exposure of the dams) for 1 of 3 exposure periods: for 28 days throughout the neonatal period, for 5 months after weaning, or during both the neonatal and postweaning periods. For all dose levels and exposure periods, no effects were observed on body weights or thyroid and

brain weights. The behavioral parameter of exploratory activity in 30-day-old weanlings was depressed ($p<0.05$) by exposure to the 10 ppm dietary level during the neonatal period, while enhanced operant learning ability in adulthood was observed for this same group of rats and also for rats exposed to 1 ppm dietary maneb during the neonatal period. Increased plasma corticosterone levels were seen in rats exposed to 0.5 or 10 ppm only during the postweaning period. Rats exposed during either the neonatal period or during the postweaning period, but not both, had statistically significant decreases of 7-23% in regional brain cholinesterase (ChE) activity at all exposure levels.

Several subchronic toxicity studies cited in the Russian literature evaluated only one or a few toxicological endpoints; since only abstracts were available for these studies, only limited details were provided. Przezdziecki et al. (1969) fed female Wistar rats 163 mg maneb/kg diet for 7 months, and observed resultant statistically significant decreases in the weight of kidneys, adrenal glands and ovaries, and an increase in thyroid weight. No effect on hematologic indices was measured, and microscopic examinations did not reveal pathological alterations in parenchymatus organs. Orlova et al. (1971) observed decreased enzyme activity in the sex glands, brain and liver of both sexes of rats following oral administration of maneb at a level of 30 mg/kg/day for 5 months. Matokhnyuk (1971) exposed rats to maneb vapors at a concentration of 300 mg/m^3 for 1 month, and observed an increase in blood pyruvate, decreases in erythrocytes, and decreases in kidney and heart succinate dehydrogenase. A concentration of 4.7 mg/m^3 was reported to be the threshold concentration for the manifestation of toxicity for inhalation exposure to maneb.

Subchronic oral administration of maneb to rats resulted in alterations of the thyroid gland and its normal functions. Following dietary administration of maneb at concentrations of 0, 250, 500, 1000 or 1500 ppm for 60 days to Osborne-Mendel rats, Sobotka (1971) observed dose-related changes in the electrophoretic pattern of soluble proteins from thyroid tissue. The adversity of these changes or their relationship to dose is not clear from the manuscript. Bankowska et al. (1970) administered dietary concentrations of 0, 500 or 5000 ppm of maneb to male rats for 6 weeks, and observed resultant gross and microscopic changes in the thyroid gland and reduced uptake of ^{124}I by the thyroid gland at both dose levels. Ivanova-Chemishanska et al. (1971) administered maneb orally as an aqueous suspension at 0.1 of the LD_{50} to 12 male albino rats daily for 30 days. Thyroid changes, determined by light and electron microscopy, included increased thyroid function and hyperplasia. These thyroid changes, in conjunction with decreased iodine concentration by the thyroid, led the authors to conclude that increased thyro- tropin stimulation induced the observed changes.

Several subchronic oral studies in rats and rabbits indicated that the blood is also a target organ for maneb toxicity. Following oral administration of maneb at a dose level of 5% of the LD_{50} to rats for 4 months, Olefir and Karpenko (1971) noted decreased protective properties of the leukocytes, particularly regarding the ability of neutrophils to digest phagocytosed microbes. Kurbat (1968) administered maneb orally at dose levels of 50-500 mg/kg/day in a 2-20% suspension in starch to male and female rabbits for up to 78 days. Leukopenia was noted over the range of dose levels, and resulted in the death of all treated animals on days 12-78 of dosing. At autopsy, multiple petechial hemorrhages were observed in the mucosa of the GI tract, in the external layers of myocardium, and under the

vesceral pleura. Karpenko et al. (1978) gave oral doses of 250 mg/kg/day maneb to rabbits for 2.5 months, and reported treatment-related swelling, fiber breaks, and hemorrhaging of the blood vessels of the heart, lungs, kidneys and skin. In a shorter term study (2-4 weeks) using the same dosing regime, Karpenko (1975) observed an increased coagulability of the blood of treated rabbits, which may explain the previously discussed hemorrhagic and thrombotic conditions observed in subchronic experiments.

5.6. OTHER RELEVANT INFORMATION

The oral LD_{50} of maneb in rats was reported to be 6750 mg/kg (NIOSH, 1983). NIOSH (1983) also reported that the lowest toxic oral dose of maneb for 11-day pregnant rats was 1000 mg/kg. Maneb exhibited high degrees of skin irritation and allergenicity and pronounced contact hypersensitivity when applied to the skin of guinea pigs (dose and duration of exposures not reported) (Matsushita et al., 1976, 1978).

Koizumi et al. (1979) reported a case study of a 62-year-old man, with no previous exposure to maneb, acutely exposed to maneb while applying the pesticide to a 200 m^2 garden. The subject had transient symptoms of oliguria, diarrhea, and hoarseness; and acute renal failure and electrocardiogram abnormalities, which were corrected by hemodialysis. About 1 week after exposure, itchy exanthema was observed on the back and abdomen of the subject.

When maintained on a diet supplemented with 5 g maneb/kg diet, female CF_1 mice were observed to have a complete inhibition of colon cancer induced by subcutaneous administration of 1,2-dimethylhydrazine (Wattenberg et al., 1977).

6. AQUATIC TOXICITY

6.1. ACUTE

Several species of fish, both freshwater and marine, have been used in acute mortality tests with maneb (usually 80-85% purity). As summarized in Table 6-1, the marine bream, Pagurus major, appears to be the most sensitive species tested. Mullet, Mugil cephalus, and bluegill sunfish, Lepomis macrochirus, were the most tolerant of maneb. The 96-hour LC_{50} values for the various species ranged from 0.18-0.99 ppm with 48- and 24-hour values ranging between 0.33-1.45 and 0.90-2.25 ppm, respectively.

Acute mortality tests with maneb have been done on several other types of aquatic organisms (Table 6-2). The LT_{50} values at various concentrations of maneb were determined for adult male and female newts, Triturus cristatus (Zaffaroni et al., 1978). Females were less sensitive, surviving almost twice as long at a given maneb concentration than males. At 125 ppm maneb, LT_{50} values for females and males were 16 and 8.8 hours, respectively. At maneb levels of 100, 75 and 50 ppm survival times were progressively longer, males consistently being more sensitive. At 25 ppm maneb, all males died within 25 days (LT_{50} = 255 hours) while some females were still alive after 5 months (Zaffaroni et al., 1978).

The 48-hour LC_{50} for the cockle (Cardium edule: Mollusk) and the starfish (Asterios rubens: Echinoderm) ranged from 100-300 ppm and 33-100 ppm maneb, respectively. Four crustaceans, the brown shrimp, Crangon crangon, the harpacticoid copepod, Nitocra spinipes, the water flea, Daphnia pulex, and the scud, Hyalella azteca, were used for acute toxicity testing of maneb (for specific data see Table 6-2). The 96-hour LC_{50} of the copepod, an important food source of many fish, was determined to be 0.11 ppm maneb (Linden et al., 1979). The LC_{50} for the mosquito larvae, Culex restuans, was high (>4900 ppm), indicating its tolerance to maneb.

TABLE 6-1

Acute Lethal Effects of Maneb to Fish

Species	Duration	Concentration (mg/ℓ)	Method	Effect	Reference
Bluegill sunfish, *Lepomis macrochirus*	24 hours	2.25	NR	LC_{50}	Schneider, 1979
	48 hours	1.45	NR	LC_{50}	Schneider, 1979
	96 hours	0.99	NR	LC_{50}	Schneider, 1979
Bleak, *Alburnus alburnus*	96 hours	0.52	static*	LC_{50}	Linden et al., 1979
Harlequin fish, *Rasbora heteromorpha*	24 hours	0.90	constant flow	LC_{50}	Tooby et al., 1975
	48 hours	0.77	constant flow	LC_{50}	Tooby et al., 1975
	96 hours	0.53	constant flow	LC_{50}	Tooby et al., 1975
Mullet, *Mugil cephalus*	96 hours	0.97	NR	LC_{50}	Igarashi et al., 1981
Marine bream, *Pagurus major*	96 hours	0.18	NR	LC_{50}	Igarashi et al., 1981
Armed bullhead, *Agonus cataphractus*	48 hours	0.33-1.0	static aerated	LC_{50}	Portmann and Wilson, 1971

*Water conditions: 10°C, 75 mg/ℓ alkalinity, pH of 7.8 and 7 ppt salinity.

NR = Not reported

TABLE 6-2

Acute Lethal Effects of Maneb to Aquatic Organisms

Species	Duration	Concentration (mg/ℓ)	Method	Effect	Reference
Female newt, *Triturus cristatus*	16 hours	125	static[a]	LT_{50}	Zaffaroni et al., 1978
	19.5 hours	100	static[a]	LT_{50}	Zaffaroni et al., 1978
	25.5 hours	75	static[a]	LT_{50}	Zaffaroni et al., 1978
	168.0 hours	50	static[a]	LT_{50}	Zaffaroni et al., 1978
Male newt, *Triturus cristatus*	8.8 hours	125	static[a]	LT_{50}	Zaffaroni et al., 1978
	11.0 hours	100	static[a]	LT_{50}	Zaffaroni et al., 1978
	19.0 hours	75	static[a]	LT_{50}	Zaffaroni et al., 1978
	76.0 hours	50	static[a]	LT_{50}	Zaffaroni et al., 1978
	255.0 hours	25	static[a]	LT_{50}	Zaffaroni et al., 1978
Cockle, *Cardium edule*	48 hours	100-330	static aerated	LC_{50}	Portmann and Wilson, 1971
Starfish, *Asterias rubens*	48 hours	33-100	static aerated	LC_{50}	Portmann and Wilson, 1971
Brown shrimp, *Crangon crangon*	48 hours	3.3-10	static aerated	LC_{50}	Portmann and Wilson, 1971
Harpacticoid copepod, *Nitocra spinipes*	96 hours	0.11	static[b]	LC_{50}	Linden et al., 1979
Water flea, *Daphnia pulex*	18 hours	94.4	static	LC_{50}	Bowman et al., 1981
Scud, *Hyalella azteca*	18 hours	96.5	static	LC_{50}	Bowman et al., 1981
Mosquito larvae, *culex restuans*	18 hours	>4900	static	LC_{50}	Bowman et al., 1981

[a]Water conditions: 18°C, pH of 7.4, 300 mg/ℓ hardness

[b]Water conditions: 10°C, 75 mg/ℓ alkalinity, pH of 7.8, 7 ppt salinity

6.2. CHRONIC EFFECTS

Bancroft and Prahlad (1973) reported that maneb at 2.5-5.0 ppm caused growth retardation, and gross and histological pathologies in Xenopus leavis (Amphibian) embryos. Reduction in size and delay or arrest of melanin development in the eye and skin were the first changes observed, followed by decreased movement and altered behavior. Histological examination revealed the decrease in melanin production, as well as enlarged and malformed notochord development. Embryos exposed at 4-5 ppm did not swim and died of starvation.

In a series of studies with the crested newt, T. cristatus carnifex, various effects of long-term exposure to maneb were reported (Zaffaroni et al., 1978, 1979; Arias and Zavanella, 1979; Zavanella et al., 1980). Newts exposed to maneb at 0.5, 2.5 and 5.0 ppm for 19-23 weeks (exposed continuously, but not fed!) or 37-40 weeks (exposed 4 days/week with feeding) had no significant changes in leucocyte counts. Male newts exposed to 5 ppm maneb, however, had a 40-60% reduction in erythroblasts (Zaffaroni et al., 1979). Maneb exposure (5 ppm) for up to 12 weeks delayed forelimb regeneration and caused skeletal deformation in the regenerated limbs (Arias and Zavanella, 1979). Vascular dilation, dermal hemorrhage and decreased pigment development were also noted. Zaffaroni et al. (1978) reported gross skin pathologies, severe renal glomerular lesions and hepatic and vascular congestion after maneb exposure (25-125 ppm). Zavanella et al. (1980) reported that maneb had no significant effect on the development of melanomas in treated newts.

6.3. PLANT EFFECTS

Pertinent data regarding the effects of maneb on aquatic plants were not located in the available literature.

6.4. RESIDUE

Pertinent data regarding maneb residues in aquatic organisms were not located in the available literature.

6.5. OTHER RELEVANT INFORMATION

Additional information regarding the toxic effects of maneb to aquatic organisms was not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee established a temporary ADI of 0-0.005 mg/kg body weight for all dithiocarbamate fungicide compounds (IARC, 1976).

Under the Federal Food, Drug and Cosmetic Act, tolerances for maneb residues have been set as follows: 2 ppm, in or on apples [37(182)FR 19134-19135]; 4 ppm, in or on bananas [37(143)FR 14783], cucumbers, melons, squash (summer and winter), and tomatoes [37(135)FR 13695-13696]; 5 ppm, in or on celery [37(135)FR 13695-13696] and sweet corn [38(30)FR 4394].

The USSR has recommended maximum permissible atmospheric exposure to maneb for humans to be set at 0.5-1 mg/m^3 (Kangas and Koskinen, 1978; Matokhnyuk, 1971).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of maneb were not located in the available literature.

8. RISK ASSESSMENT

Maneb has been well tested for carcinogenicity in mice and rats. Equivocal results were obtained for the incidence of lung adenomas in four strains of mice and the small number of rats surviving treatment. Maneb was positive in genotoxicity assays of reverse mutation in E. coli Strain B (Warren et al., 1976), mitotic gene conversion in S. cerevisiae (Warren et al., 1976; Guerzoni et al., 1976), and scheduled and unscheduled DNA synthesis in mammalian cell cultures (Rocchi et al., 1980). IARC (1976, 1982) concluded that the evidence is not sufficient to class maneb as a carcinogen in experimental animals. However, there is sufficient evidence that ETU, a degradation product and metabolite of zineb, is carcinogenic in experimental animals (IARC, 1974, 1982; 42 FR 40618). Moreover, the Carcinogen Assessment Group (CAG) of the U.S. EPA conducted a risk assessment for ethylenebisdithiocarbamate (EBDC) on the basis that a contaminant and metabolite, ETU, was carcinogenic (U.S. EPA, 1979). Because ETU is also a metabolite and an environmental degradation product of zineb, a risk assessment similar to the previous one should be considered.

Fetotoxic and teratogenic effects were observed in the fetuses of rats given maneb orally at dose levels ≥250 mg/kg during gestation (Petrova-Vergieva and Ivanova-Chemishanska, 1973; Larson et al., 1976; Chernoff et al., 1979), while only fetotoxicity was observed in mice given maneb orally at dose levels ≥240 mg/kg (Chernoff et al., 1979). Sobotka et al. (1972) administered dietary concentrations of maneb at 0, 0.5, 1.0 or 10 ppm to male Osborne-Mendel rats for 5 months after weaning. The number of animals treated at the 1.0 ppm level was considered insufficient, and, therefore, results for this group were not reported. Increased plasma cortisone levels and decreased brain ChE activity was observed at both 0.5 and 10 ppm;

enhanced operant learning ability was observed at the high dose. However, the adversity of these latter effects, and, therefore the usefulness of these particular data for a toxicity risk assessment is not readily apparent. Nor were histological effects looked for in this latter study. Oral administration of maneb to rats at dose levels of 5-30 mg/kg bw/day for up to 11-12 months induced numerous reproductive defects of varying severity in both sexes of treated animals (Shtenberg et al., 1969, 1973). Additional oral subchronic studies of Przezdziecki et al. (1969), Orlova et al. (1971), Sobotka (1971), Bankowska et al. (1970), Kurbat (1968) and Karpenko et al. (1978) do not report doses that cause adverse effects lower than that described by Shtenberg et al. (1969) at 5 mg/kg bw/day for 11-12 months.

Although these latter subchronic studies, as well as Shtenberg et al. (1969, 1973), are only reported as abstracts, collectively they constitute a body of data useful for estimating an ADI. It appears that the most appropriate study on which to base an ADI for maneb is that of Shtenberg et al. (1969). The chosen dose, 5 mg/kg/day, represents the LOAEL (lowest-observed-adverse-effect level) from the total data base. The ADI is estimated as follows:

$$\text{ADI} = \frac{5 \text{ mg/kg/day} \times 70 \text{ kg}}{1000}$$

$$= 0.35 \text{ mg/day}$$

where 70 kg is the assumed body weight of the average person and the 1000-fold uncertainty factor represents a 10-fold factor each for both intra- and interspecies adjustment for the differences in responsiveness to the toxicity of maneb, and a 10-fold factor because the ADI is based on a LOAEL and not a NOAEL according to previous guidelines (45 FR 79353). Note here that

the study is judged to be of sufficient duration such that an additional uncertainty factor because of length of the study is not needed.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment, however, can be presented in this document.

The CBI Appendix to this document reviews subchronic and chronic studies of dietary maneb exposure in animals that provide a more realistic and more complete picture of maneb toxicity then do the limited data obtained from abstracts of studies from the Russian literature. An ADI of 1.61 mg/day for a 70 kg man (0.023 mg/kg/day), based on a NOEL of 30 ppm of maneb in the diet (equivalent to 2.3 mg/kg/day, based on food consumption and weight gain data) in a 31-month study in rats and an uncertainty factor of 100, is recommended. A dietary level of 100 ppm (equivalent dose not available) in a subchronic study in rats, associated with increased severity of thyroid hyperplasia, was the LOAEL.

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APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

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